TRAITÉ DE COOPÉRATION EN MATIÈRE DE BREVETS

PCT

RAPPORT PRÉLIMINAIRE INTERNATIONAL SUR LA BREVETABILITÉ

(chapitre I du Traité de coopération en matière de brevets)

(règle 44*bis* du PCT)

Référence du dossier du déposant ou du mandataire U34-19925 WO	**POUR SUITE À DONNER**	Voir le point 4 ci-dessous
Demande internationale no. PCT/FR2004/050631	Date du dépôt international *(jour/mois/année)* 30 November 2004 (30.11.2004)	Date de priorité *(jour/mois/année)* 02 December 2003 (02.12.2003)
Classification internationale des brevets (8°edition, sauf indication d'une #dition ant#rieure) Voir les informations pertinentes dans le formulaire PCT/ISA/237		
Déposant UNIVERSITE FRANCOIS RABELAIS		

1. Le présent rapport préliminaire international sur la brevetabilité (chapitre I) est établi par le Bureau international au nom de l'administration chargée de la recherche internationale selon la règle 44*bis*.1.a).

2. Ce RAPPORT comprend un total de 9 feuilles, y compris la présente feuille de couverture.

   Dans les feuilles jointes, toute référence à l'opinion écrite de l'administration chargée de la recherche internationale doit être entendue, à la place, comme une référence au rapport préliminaire international sur la brevetabilité (chapitre I).

3. Le présent rapport contient des indications relatives aux points suivants :

☒	Cadre n° I	Base de l'opinion
☐	Cadre n° II	Priorité
☐	Cadre n° III	Absence de formulation d'opinion quant à la nouveauté, l'activité inventive et la possibilité d'application industrielle
☐	Cadre n° IV	Absence d'unité de l'invention
☒	Cadre n° V	Déclaration motivée selon l'article 35.2) quant à la nouveauté, l'activité inventive et la possibilité d'application industrielle; citations et explications à l'appui de cette déclaration
☐	Cadre n° VI	Certains documents cités
☐	Cadre n° VII	Certaines irrégularités relevées dans la demande internationale
☐	Cadre n° VIII	Certaines observations relatives à la demande internationale

4. Le Bureau international communiquera le présent rapport aux offices désignés conformément aux règles 44*bis*.3.c) et 93*bis*.1 mais pas avant l'expiration du délai de 30 mois à compter de la date de priorité (règle 44*bis*.2), sauf si le déposant a présenté une requête expresse à cet égard en vertu de l'article 23.2).

	Date d'établissement du présent rapport 29 August 2006 (29.08.2006)
Bureau international de l'OMPI 34, chemin des Colombettes 1211 Geneva 20, Switzerland no de télécopieur +41 22 338 82 70	Fonctionnaire autorisé Beate Giffo-Schmitt e-mail: pt03@wipo.int

Formulaire PCT/IB/373 (janvier 2004)

PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	See Form PCT/ISA/210 (sheet 2)
Applicant's or agent's file reference: U34-19925 WO	FOR FURTHER ACTION: See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/FR2004/050631	30.11.2004	02.12.2003

International Patent Classification (IPC) or both national classification and IPC
C12N15/86 A61 K48/00 C12N7/01 A61 P35/00

Applicant
UNIVERSITE FRANCOIS RABELAIS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/EP	Authorized officer
Facsimile No.	Telephone No.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/FR2004/050631

Box No. I **Basis of this opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☒ in written format

      ☒ in computer readable form

   c. time of filing/furnishing

      ☒ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/FR2004/050631

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-24	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-24	NO
Industrial applicability (IA)	Claims	1-24	YES
	Claims		NO

2. Citations and explanations:

Reference is made to the following documents:

D1: LEBEDEVA IRINA ET AL: "Infectious particles derived from Semliki forest virus vectors encoding murine leukemia virus envelopes" JOURNAL OF VIROLOGY, vol. 71, no. 9, 1997, pages 7061-7067, XP002284768 ISSN: 0022-538X

D2: WO 03/072771 A (PASANEN TUENA; WAHLFORS JARMO (FI)) 4 September 2003 (2003-09-04)

D3: LUNDSTROM KENNETH: "Alphavirus vectors as tools in cancer gene therapy." TECHNOLOGY IN CANCER RESEARCH & TREATMENT. UNITED STATES FEB 2002, vol. 1, no. 1, February 2002 (2002-02), pages 83-88, XP001182046 ISSN: 1533-0346

The present application fails to comply with the requirements of PCT Article 33(1) since the subject matter of claims 1 to 24 does not involve an inventive step as defined in PCT Article 33(3).

1. Document D1 is considered to be the prior art closest to the subject matter of claim 3.
D1 describes a viral particle comprising the

SrepβGal construct (cf. figure 1 of D1) and envelope molecules of a retrovirus (Moloney murine leukemia virus, MLV) (cf. D1, page 7063, the paragraph entitled "infectious particle formation"). Said construct is derived from the SEMLIKI forest virus and does not contain the structural genes of said virus.
This viral particle differs from the viral particle of claim 3 in that it contains a structural element derived from an alpha virus, the capsid of the SEMLIKI forest virus.

The problem solved by claim 3 can thus be considered to be the provision of a viral particle which can be obtained while avoiding any risk of recombination that can generate replicative particles in the producer lines.
The technical problem retained corresponds to that identified by the applicant (cf. page 3, lines 26 to 29 of the present application).

The technical problem is solved by the present claim 3 if one considers that the elimination of the risk of recombination between the alpha-virus-derived vector and the gene encoding the alpha-virus capsid solves said problem.

A person skilled in the art seeking to solve the technical problem mentioned above has two possibilities: deleting the gene encoding the capsid in the packaging cells or using other structural

elements.

D1 shows that the capsid of the SEMLIKI forest virus is not necessary for the formation of infectious particles if the packaging is carried out in the presence of MLV envelope protein (cf. D1, page 7065, paragraph entitled "SFV capsid is not necessary for formation of infectious particles").
A person skilled in the art thus automatically concludes therefrom that it is possible to solve the technical problem quite simply by eliminating the SEMLIKI forest virus capsid.

Claim 3 thus does not involve an inventive step (PCT Article 33(3)).

The objection applies *mutatis mutandis* to claims 1, 4 and 6.

2. Similar reasoning (same closest prior art, same technical problem) applies to claim 2, combining D1 and D2, which describes viral particles containing an alpha-virus-derived vector having the VSV-G protein as the only structural element (cf. examples 1 to 4 of D2). A person skilled in the art, on reading D2, would know that it is possible to replace the SEMLIKI forest virus capsid and the MLV envelope with the VSV-G protein.

Claim 2 thus does not involve an inventive step (PCT Article 33(3)).

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3. Similar reasoning (same closest prior art, same technical problem) applies to claim 5. When seeking a solution for eliminating/replacing the SEMLIKI forest virus capsid, it is obvious to a person skilled in the art that the chosen capsid must be compatible, firstly, with the envelope and, secondly, with the vector. A person skilled in the art is in no doubt that envelope/capsid pairs originating from the same virus are compatible. Since the MLV envelope is used in D1, the use of the MLV capsid thus cannot pose a problem with regard to the envelope/capsid interactions. Moreover, the sequences for encapsidation of a given vector with the MLV capsid are well known in the art; it involves in particular the extended packaging sequence of MLV viruses.

Claim 5 thus does not involve an inventive step (PCT Article 33(3)).

4. Dependent claims 7 and 8 do not contain any feature which, in combination with the features of any one of the claims to which they refer, meets the requirements of the PCT in respect of inventive step, see documents D1 and D2 and the corresponding passages cited in the search report.
It may in particular be noted that a mutated p26S promoter does not necessarily correspond to a p26S promoter which has reduced promoter activity. As a result, the advantages possibly associated with the use of a p26S promoter which has reduced promoter activity cannot be taken into account in judging the

inventive step of claim 8.

In the case of claim 7, the problem solved by the eukaryotic promoter positioned in the 5'-position is not identifiable. The usefulness of said promoter in the constructs resulting in the generation of the viral particles is indicated in the application on page 7, lines 7 to 13. However, according to the indications provided in said passage, the promoter serves to express the alpha-virus-derived vector and thus is not on the latter. It thus should not be present in the viral particle.

5. The inventive step objections directed against claims 1 to 8 apply *mutatis mutandis* to the corresponding methods for production. These are the methods of claims 12, 13, 16, 17 and 20 to 24.
In the absence of arguments demonstrating the contrary, the remaining claims relating to methods for production (claims 14, 15, 18 and 19) do not appear to contain any features which, in combination with the features of any one of the claims to which they refer, meet the requirements of the PCT in respect of inventive step, see documents D1 and D2 and the corresponding passages cited in the search report.

6. The viral particles of claims 1 to 8 are generated in an obvious manner so as to infect eukaryotic cells *in vitro*; claim 9 thus cannot involve an inventive step in view of the absence of inventive step of the viral particles of claims 1 to 8 (PCT Article 33(3)).

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

7. The use, for the treatment of cancer, of viral particles, in particular of particles of retroviral type or of particles containing VSV-G alone, containing an alpha-virus-derived vector made replication-defective by deletion, or replacement with at least one transgene, of the structural genes, is well known in the art (cf., for example, D3, figures 1 and 3, the introduction from page 83 to page 84 and the paragraph entitled "Production of retrovirus-like particles" and D2, page 6, lines 19 to 25). Claims 10 and 11 thus cannot involve an inventive step in view of the lack of inventive step of the viral particles of claims 1 to 8 (PCT Article 33(3)).